

d) replicating said operatively linked subset to form an enriched collection of replicated molecules; and

D1 e) detecting one or more nucleotide sequence differences in the members of said collection of step (d) with a method that detects one or more nucleotide differences with respect to a reference sequence,

wherein said steps (b) and (c) follow step (a) but can occur in either order, followed thereafter by steps (d) and (e) in that order, wherein said steps (a)-(e) enrich for and identify a nucleic acid sequence difference with respect to a reference sequence.

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69. (Twice amended) A method of enriching for and identifying nucleic acid sequence differences with respect to a reference sequence comprising:

a) fragmenting a genomic nucleic acid sample from one or more individuals;

D2 b) physically separating a subset of said nucleic acid fragments based on the size of the fragments;

c) detecting one or more nucleic acid sequence differences with respect to a reference sequence in the members of said separated molecules of step (b), wherein steps (a)-(c) enrich for and identify a nucleic acid sequence difference with respect to a reference sequence.

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157. (Amended) A method of enriching for and identifying a nucleic acid sequence difference with respect to a reference sequence comprising:

D3 a) contacting a nucleic acid sample with a DNA binding domain of a restriction endonuclease that cleaves said nucleic acid sample 300,000 times or fewer, wherein said sample comprises a subset of nucleic acid molecules having a sequence that is bound by said DNA binding domain, and wherein a bound subset of nucleic acid molecules is retained by said DNA binding domain, such that the subset of bound nucleic acid molecules is enriched for molecules comprising the sequence recognized by said DNA binding domain; and